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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,779	08/20/2001	Keisuke Teshigawara	3813-0101P	6309

2292 7590 08/28/2002

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/868,779	TESHIGAWARA ET AL.
Examiner	**Art Unit**
Anne M Wehbé	1632

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s) _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

Applicant's amendment and response received on 6/3/02 has been entered. Claims 1-8 have been canceled. New claims 9-20 have been added. Claim 9-20 are currently under examination in the instant application. Please note that the examiner of record in this case has changed, see page 10. An action on the merits follows.

Those sections of Title 35, US code, not included in this action, can be found in the previous office actions.

Claim Rejections - 35 USC § 112

The rejection of canceled claims 5-8 under 35 U.S.C. 112, first paragraph, is maintained over new claims 15-20. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the previous examiner has asserted that the specification fails to show the experimental data regarding the expression of B7 gene in K562 cells. The previous examiner made no such assertion. The previous office action stated that the basis for rejection of these composition claims was in the non-enablement of the specification for the claimed intended

use of the compositions for immune therapy as recited in the preamble of the claims. The previous office action did not include the methods of *in vitro* culture in the enablement rejection or question whether the specification enables K562 cells which express B7. By not including the *in vitro* methods in this rejection, the office has already acknowledged that the specification is enabling for the disclosed *in vitro* culture methods. The issue at hand is the lack of enablement for *in vivo* immune therapy.

The applicant also states that the previous office action has only addressed one of the factors identified as relevant to enablement under 35 U.S.C. 112 in *In re Wands*, the lack of working examples. This is an incorrect evaluation of the previous office action. the previous office action analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement for the instant methods. In addition, case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and Ex parte Sudilovsky 21 USPQ2d 1702). Further, the applicant is reminded that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). As discussed in detail in the previous office action, the lack of enablement for immune therapy in the

instant specification is specifically related to the underdeveloped and unpredictable state of the art of immune therapy at the time of filing (see Hernberg et al., Porgador et al., and Atzpodien et al.), the lack of guidance provided in the specification for immune therapy of disease such as cancer using the claimed anti-cancer lymphocytes, the lack of working examples which demonstrate a therapeutic effect on any disease including cancer following the administration of the disclosed lymphocytes to any mammal, and the breadth of the claims. The applicant has not addressed any of the issues in their response. Therefore, the instant grounds of rejection are maintained over claims 15-20.

The rejection of claims 1-8 under 35 U.S.C. 112, second paragraph for indefiniteness is withdrawn in view of the cancellation of these claims. However, please note that new claims 14 and 20 are subject to new grounds of rejection under 35 U.S.C. 112, second paragraph, presented below.

New claims 14 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite, ".. wherein said lymphocytes are activated by an immunomodulator to enhance cancer cell killing activators". It is unclear what is meant by "cancer cell killing activators". The choice of language renders the claim confusing as to whether the immunomodulator simply increases the ability of the lymphocytes to kill tumor cells, or

whether the immunomodulators are supposed to increase the ability of the lymphocytes to stimulate or increase the activity of other non-lymphocyte associated "activators".

Claim Rejections - 35 USC § 103

The rejection of claims 1-4 under 35 U.S.C. 103 is withdrawn in view of applicant's cancellation of the claims.

The following new grounds of rejection apply to applicant's new claims 9-20.

Claim Rejections - 35 USC § 102

New claims 9-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Kim et al. (Jan. 1999), Vol. 47, 257-264. The applicant claims methods of culturing anti-cancer lymphocytes *in vitro* comprising incubating lymphocytes with cancer cells under conditions to amplify NK cells or MHC-bound antigen specific killer T cells, and compositions for use in immune therapy comprising anti-cancer lymphocytes obtained using said methods. The applicant further claims said methods and compositions wherein the cancer cell is class I positive, or has lower levels of class I antigen expression, wherein the cancer cells express B7, wherein the lymphocytes are collected from peripheral blood, or wherein the lymphocytes are activated by an

immunomodulator to enhance cancer cell killing activators. In regards to the composition claims, claim 15-20, please note that the intended use of the composition, "for immune therapy", is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." *In re Casey*, 152 USPQ 235 (CCPA 1967); *In re Otto* , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02). In addition, claims 15-20 are product-by-process claims. However, in product by process claims, the process used to create the product must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Case law states that "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable though the prior product was made by a different process." *In re Thorpe*, 777F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is

upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, for the purpose of analysis under 102 and 103, the applicant's claims 15-20 read on a composition of anti-cancer lymphocytes.

Kim et al. teaches an improved method for generating tumor-antigen specific T cells using an in vitro culture system in which primary T cells are mixed with transduced MCA205 tumor cells that express B7.1 and cultured in the presence of the immunomodulatory cytokine IL-2 (Kim et al., page 259-260). Please note that the spleens used to purify the primary T cells comprises peripheral blood. Kim et al. further teaches that other tumor transduced to express B7 besides MCA205 can be used, such as CT26, A20, and B16 (Kim et al., page 262). Figure 3 of Kim et al. demonstrates that the T cells produced using this method are capable of tumor-specific MHC class I restricted killing of tumor cells in a CTL assay (Kim et al., page 261). Kim et al. further demonstrates that the tumor-specific lymphocytes generated using the Kim method are effective in inhibiting tumor growth following adoptive transfer (Kim et al., page 261, Table 1). Thus, by teaching all of the elements of the claims, Kim et al. anticipates the instant invention.

New claims 9-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al. (1996) J. Immunol., Vol. 156, 1117-1125. The applicant claims methods of culturing anti-cancer lymphocytes in vitro comprising incubating lymphocytes with cancer cells under conditions to

amplify NK cells or MHC-bound antigen specific killer T cells, and compositions for use in immune therapy comprising anti-cancer lymphocytes obtained using said methods. The applicant further claims said methods and compositions wherein the cancer cell is class I positive, or has lower levels of class I antigen expression, wherein the cancer cells express B7, wherein the lymphocytes are collected from peripheral blood, or wherein the lymphocytes are activated by an immunomodulator to enhance cancer cell killing activators. In regards to the composition claims, claim 15-20, please note that the intended use of the composition, "for immune therapy", is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02). In addition, claims 15-20 are product-by-process claims. However, in product by process claims, the process used to create the product must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Case law states that "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable though the prior

product was made by a different process." *In re Thorpe*, 777F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, for the purpose of analysis under 102 and 103, the applicant's claims 15-20 read on a composition of anti-cancer lymphocytes.

Liu et al. teaches an improved method for generating tumor-antigen specific T cells using an in vitro culture system in which primary T cells are mixed with transfected tumor cells that express B7.1 and cultured in the presence of the immunomodulatory cytokines IL-2 and IL-4 (Liu et al., page 1118). Please note that the spleens used to purify the primary T cells comprises peripheral blood. Liu et al. also teaches that sources of primary T cells include peripheral blood lymphocytes and tumor-infiltrating lymphocytes (Liu et al., page 1124). Liu et al. particularly teaches the use of transfected P815, El4, LLC, and K1735 tumor cells which express MHC class I and B7 (Liu et al., page 1119, Figure 1). Figure 1 also shows that the LLC tumor expresses lower than normal levels of MHC class I (Liu et al., page 1119, Figure 1). Figures 2-4 and 6 of Liu et al. demonstrates that the T cells produced using this method are capable of tumor-specific MHC

class I restricted killing of tumor cells in a CTL assay (Liu et al., pages 1119-1120). Thus, by teaching all the elements of the claims, Liu et al. anticipates the instant invention.

No claim are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER